Research Article
Cirrhosis and Liver Failure

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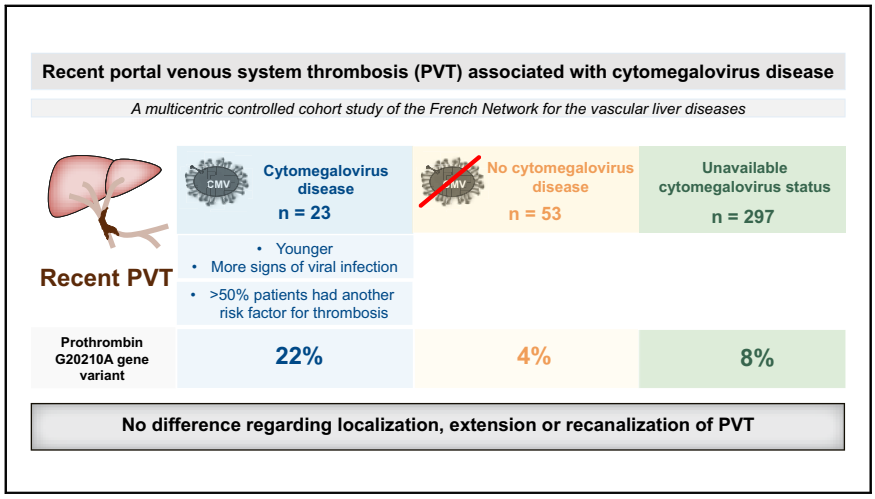
Multicenter study on recent portal venous system thrombosis associated with cytomegalovirus disease

Graphical abstract



Highlights

- Patients with CMV-associated PVT were younger, had higher heart rate and body temperature, and elevated serum ALT.
- The prothrombin G20210A gene variant is associated with CMV disease in patients with PVT.
- Diagnosing CMV disease in a patient with PVT does not deter from performing a complete screening of risk factors for thrombosis.
- CMV disease might trigger PVT in susceptible patients.
- Patients with CMV-associated PVT have similar thrombosis extension and outcome as patients with PVT without CMV disease.

Authors

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Lay summary

Patients with cytomegalovirus (CMV)-associated portal venous system thrombosis have similar thrombosis extension and evolution as patients without CMV disease. However, patients with CMV-associated portal venous system thrombosis more frequently have the prothrombin G20210A gene variant, suggesting that these entities act synergistically to promote thrombosis.

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Multicenter study on recent portal venous system thrombosis associated with cytomegalovirus disease

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Background & Aims: Recent non-malignant non-cirrhotic portal venous system thrombosis (PVT) is a rare condition. Among risk factors for PVT, cytomegalovirus (CMV) disease is usually listed based on a small number of reported cases. The aim of this study was to determine the characteristics and outcomes of PVT associated with CMV disease.

Methods: We conducted a French multicenter retrospective study comparing patients with recent PVT and CMV disease ("CMV positive"; n = 23) to patients with recent PVT for whom CMV testing was negative ("CMV negative"; n = 53) or unavailable ("CMV unknown"; n = 297).

Results: Compared to patients from the "CMV negative" and "CMV unknown" groups, patients from the "CMV positive" group were younger, more frequently had fever, and had higher heart rate, lymphocyte count and serum ALT levels ($p \leq 0.01$ for all). The prevalence of immunosuppression did not differ between the 3 groups (4%, 4% and 6%, respectively). Extension of PVT was similar between the 3 groups. Thirteen out of 23 "CMV positive" patients had another risk factor for thrombosis. Besides CMV disease, the number of risk factors for thrombosis was similar between the 3 groups. Heterozygosity for the prothrombin G20210A gene variant was more frequent in "CMV positive" patients (22%) than in the "CMV negative" (4%, $p = 0.01$) and "CMV unknown" (8%, $p = 0.03$) groups. Recanalization rate was not influenced by CMV status.

Conclusions: In patients with recent PVT, features of mononucleosis syndrome should raise suspicion of CMV disease. CMV disease does not influence thrombosis extension nor recanalization. More than half of "CMV positive" patients have another risk factor for thrombosis, with a particular link to the prothrombin G20210A gene variant.

Lay summary: Patients with cytomegalovirus (CMV)-associated portal venous system thrombosis have similar thrombosis extension and evolution as patients without CMV disease. However, patients with CMV-associated portal venous system thrombosis more frequently have the prothrombin G20210A gene variant, suggesting that these entities act synergistically to promote thrombosis.

Introduction

Recent non-malignant non-cirrhotic extrahepatic portal venous system thrombosis (PVT) is characterized by new occurrence of a thrombus in the main portal vein and/or its right or left branches and/or splenic or mesenteric veins.[1] The incidence of PVT is estimated to be 0.7 per 100,000 per year.[2] Recent PVT can lead to intestinal infarction in 2 to 20% of cases with an estimated mortality of 20% at 30 days.[3] The causes for PVT include inherited thrombophilia (protein C or S or antithrombin deficiency; factor V or factor II gene mutation), acquired thrombophilia (antiphospholipid antibodies, myeloproliferative neoplasms, paroxysmal nocturnal hemoglobinuria), hormonal factors, as well as local and systemic inflammation.[4,5]

Human cytomegalovirus (CMV) infection is very frequent, usually without overt symptoms. Anti-CMV IgG, representing

Keywords: cavernoma; vascular liver disease; factor II gene mutation; thrombosis; immunocompetent; infection; recanalization; thrombophilia; cytomegalovirus; CMV; prothrombin.
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past infection, are found in 50-65% of adults in developed countries, and in more than 90% in developing countries.[6] After primary infection, CMV establishes a latent infection from which intermittent reactivation can occur, as with other *Herpesviridiae*.[7,8] Reinfection with new strains is also possible. CMV infection is defined by the evidence of CMV (plasma or organ-specific PCR) with or without symptoms, whereas CMV disease is defined by CMV infection with organ injury or clinical symptoms suggestive of the disease. Clinical manifestations depend on patient immunity. In immunocompromised patients and newborns, organ injury is more common.[9] In immunocompetent patients, viral replication is frequently asymptomatic, although CMV disease is possible.[10] CMV infection has been associated with indirect effects, such as increased all-cause mortality, increased risk of cardiovascular disease and increased risk of deep vein thrombosis and pulmonary embolism.[11–16]

Recent PVT associated with CMV infection has only been described in few case reports so that the specificities of this association are unknown.[17,18] The aim of this retrospective multicenter study was to describe the characteristics, associated causes and outcome of patients with CMV-associated recent PVT.

Patients and methods

Inclusion criteria

This retrospective study included 3 groups of patients with recent PVT.

The group of patients with recent PVT and CMV disease, referred to as "CMV positive" group, included all patients with CMV-associated recent PVT diagnosed between January 2000 and December 2019 in one of the centers of the French network for Vascular Liver Diseases. Diagnosis of CMV disease was based on laboratory tests performed within 3 months before or after the diagnosis of recent PVT. Details are presented in the supplementary methods.[19–21]

The group of patients with recent PVT without CMV disease, referred to as "CMV negative" group, included all patients with recent PVT, diagnosed between January 2014 and December 2019, at the French Reference Center for Vascular Liver Diseases (Hôpital Beaujon, Clichy) who tested negative for CMV. The absence of CMV disease was based on undetectable anti-CMV IgM and/or undetectable plasma CMV DNA, within 3 months before or after PVT diagnosis.

The group of patients with recent PVT untested for CMV disease, referred to as "CMV unknown" group, included patients with a diagnosis of recent PVT between January 2004 and December 2019 in one of the centers of the French network for Vascular Liver Diseases, without available CMV viral load or serology within 3 months before or after diagnosis of PVT.

The study was performed in accordance with the ethical guidelines of the 1975 Declaration of Helsinki and was approved by the institutional review board (CPP Ile de France IV, Paris; France). Informed consent was obtained from all patients included in the study.

Liver surface nodularity quantification

Liver surface nodularity (LSN) quantification was performed on portal venous phase CT images using semiautomated CT software (LSN Software, version 0.88; Liver Nodularity llc) by an abdominal radiologist (RS) blinded to clinical data, using a method explained by De Vos *et al.* in[22] and detailed in the supplementary methods.

The optimal cut-off value of 2.5 was chosen, based on previously published data, as reliably differentiating the presence or absence of advanced fibrosis.[23–26]

Definitions

Diagnostic criteria for recent PVT included imaging evidence of solid material in one or more segment(s) of the portal venous system (portal trunk, left or right portal branch, splenic vein, superior or inferior mesenteric vein) on a CT-scan or MRI, associated with signs of a recent thrombosis: hyperdense thrombus on unenhanced CT phase and/or recent abdominal pain and/or systemic inflammatory response syndrome at diagnosis. Date of diagnosis of PVT was the date of the first imaging procedure fulfilling PVT diagnostic criteria. Patients with one of the following conditions at PVT diagnosis were not included in the study: cirrhosis, portal cavernoma, variceal bleeding, hepatic or biliary malignancies.

In patients from the "CMV positive" and "CMV negative" groups, the absence of cirrhosis was ascertained using either the results of a liver biopsy, or the association of at least 2 out of the 3 following criteria: LSN <2.5; no cause for cirrhosis; liver stiffness measurement using Fibroscan® <10 kPa (Fig. S1). In patients from the "CMV unknown" group, the absence of cirrhosis was based on the opinion of the practitioner in charge of the patient.

Other definitions are presented in the supplementary methods.

Investigations for risk factors of thrombosis

Investigations for risk factors of thrombosis are detailed in the supplementary methods.[27]

Statistical analysis

Quantitative variables were expressed as median (interquartile ranges) and were compared using the Mann-Whitney test. Qualitative variables were expressed as absolute and relative (percentage) frequencies and compared using the Chi-square or the Fisher's test, as appropriate. To reduce the risk of bias, we performed sensitivity analyses comparing "CMV positive" patients with "CMV negative" and "CMV unknown" patients, matched 1:1 and 1:4, respectively, using a propensity score. Covariables included in the propensity score model were selected based on their known associations with PVT development, namely age and body mass index.[28] The model was then used to obtain matches using the nearest-neighbor matching method, with a maximal difference of propensity score of 0.05.[29]

We analyzed variables associated with complete recanalization of portal venous system thrombosis using Cox regression univariate analysis. Variables achieving a p value below 5% by univariate analysis and with less than 5% missing data were included in a Cox regression multivariate analysis.[27–29] Duration of follow-up used for these Cox regression models was the time period between PVT diagnosis and the first CT-scan or MRI showing a complete recanalization of the portal venous system, or – in the absence of recanalization – the last imaging procedure performed within 24 months after PVT diagnosis, or death if it occurred within 24 months after PVT diagnosis. Cumulative incidence of complete recanalization of the portal venous system was assessed using the Kaplan-Meier method and compared using the log-rank test.

All tests were bilateral and performed with a first-species risk of 0.05. Statistical analyses were performed using SPSS version 22.0 software (SPSS Inc., Chicago, IL).

Results

Study population

"CMV positive" group

Twenty-three patients were included in the "CMV positive" group (Clichy, n = 16; Caen, n = 2; Lille, n = 2; Besançon, n = 1; Paris Cochin, n = 1; Toulouse, n = 1) (Fig. S2). Their virological characteristics are summarized in Table S1.

Fifteen patients had confirmed CMV disease: 13 had confirmed primary infection (11 had positive anti-CMV IgM antibodies with low avidity IgG; 2 had seroconversion); 1 immunocompromised patient (Patient 1) had colitis and plasma CMV DNA at 4.61 LogUI/ml; and 1 (Patient 13) had colitis, colon biopsies with detectable CMV DNA and histological lesions compatible with CMV disease. Eight patients had probable CMV disease, based on positive anti-CMV IgM at diagnosis, but unavailable avidity. Plasma CMV DNA was available in 3 of them and was detectable in all cases. Out of the 8 patients with probable CMV disease, neutrophil to lymphocyte ratio was below 1 in 6 patients, and Downey cells were observed in 4 patients (including 1 with a neutrophil to lymphocyte ratio above 1). These proportions were similar to those observed in patients with confirmed CMV disease: 5 out of 13 had a neutrophil to lymphocyte ratio below 1 (unavailable in 2) and 4 out of 11 had Downey cells (unavailable in 4). A recent Epstein-Barr virus infection was ruled out by positive anti-EBNA IgG in the 6 patients with probable CMV disease who were tested. The supplementary results and Table S2 detail characteristics of PVT, including features related to the recentness of the thrombus.

"CMV negative" and "CMV unknown" groups

In 53 patients with recent PVT, CMV disease could be ruled out ("CMV negative" group): 48 had undetectable anti-CMV IgM antibodies and 23 had undetectable plasma CMV DNA. In 297 patients with recent PVT, neither CMV serology nor viral load at the diagnosis of PVT was available, so these patients were included in the "CMV unknown" group.

Characteristics at diagnosis of PVT

Patient characteristics are presented in Table 1 and Table S3. None of the patients from the "CMV positive" and "CMV negative" groups and 3 patients from the "CMV unknown" group were receiving anticoagulation at the time of PVT diagnosis. Patients with CMV disease were younger at the time of PVT diagnosis than patients from the "CMV negative" and "CMV unknown" groups. "CMV positive" patients more commonly had signs of viral infection including tachycardia, fever and elevated transaminases and lymphocytes than patients from the control groups. Similar results were obtained when restricting the "CMV unknown group" to patients with available liver stiffness measurement (Table S4). Similar results were also obtained when matching, using a propensity score, "CMV positive" patients with "CMV negative" and "CMV unknown" patients (Table S5). There was no difference in site or extension of PVT nor in rate of immunosuppression between "CMV positive" patients and patients from the 2 control groups.

Risk factors for thrombosis

Heterozygosity for the prothrombin G20210A gene variant was 3- to 5-fold more frequent in patients from the "CMV positive" group than in patients from the 2 control groups (Table 2, Fig. 1). Anti-cardiolipin antibodies were more commonly present at the time of PVT diagnosis in the "CMV positive" group, but these antibodies disappeared in all but 1 patient, 3 months after CMV disease. There was no difference in other risk factors for thrombosis. Besides CMV disease, the number of risk factors for thrombosis was similar between the 3 groups. Similar results were obtained when restricting the analysis to patients in the "CMV unknown group" with available liver stiffness measurement (Table S4). Similar results were also obtained when matching, using a propensity score, "CMV positive" patients with "CMV negative" and "CMV unknown" patients (Table S5).

Evolution of patients according to CMV status

Complete recanalization of the portal venous system

Twenty patients from the "CMV positive" group and 42 patients from the "CMV negative" group had one or more cross-sectional imaging (CT scan or MRI) assessment during follow-up, allowing for reliable analysis of PVT recanalization. The median duration between PVT diagnosis and last cross-sectional imaging was 16 months (3-44) and 13 months (8-24) in patients from the "CMV positive" and "CMV negative" groups, respectively (p = 0.789). The number of abdominal cross-sectional imaging (CT scan or MRI) assessments in the first 24 months was similar between "CMV positive" and "CMV negative" patients (1 [1-2], *vs.* 2 [0-2], respectively; p = 0.320). Out of these 20 CMV positive and 42 CMV negative patients, anticoagulation was initiated at the time of PVT diagnosis in all but one (Patient 1). In the latter patients, total duration of anticoagulation was 17 months (5-54) and 24 months (12-34), respectively (p = 0.696). Twelve patients interrupted anticoagulation during follow-up, including 6 of the 20 "CMV positive" and 6 of the 42 "CMV negative" group. During the first 24 months after PVT diagnosis, 10 (50%) patients in the "CMV positive" group and 12 (27%) in the "CMV negative" group had a complete recanalization of the portal venous system (p = 0.155). Cumulative incidence of complete recanalization of the portal venous system at 12 and 24 months of follow-up was 47% and 58% in the "CMV positive" group *vs.* 24% and 50% in the "CMV negative" group (Fig. S3). We performed a univariate (Table S6) and then a multivariate analysis to identify variables associated with complete recanalization of PVT at 24 months. As shown in Table 3, the only variable independently predicting complete recanalization of PVT at 24 months was a lower number of occluded segments at diagnosis. Similar results were obtained when matching, using a propensity score, "CMV positive" patients with "CMV negative" patients (Table S7). Individual outcome of the patients from the "CMV positive" group, including duration of anticoagulation, is detailed in Fig. S4.

Extension of PVT

Two patients from the "CMV positive" group developed an extension of PVT. Patient 1 had obliterative portal venopathy and colitis at diagnosis of inferior mesenteric vein thrombosis. He was initially the only patient not treated with anticoagulation and he developed an extension of thrombosis to the portal trunk 2 months later. Patient 5 had no risk factors for thrombosis apart from CMV at diagnosis of PVT (involving superior mesenteric vein, splenic vein and portal trunk thrombosis). Despite anticoagulation, he developed a left portal branch thrombosis at month 33. A myeloproliferative neoplasm was then diagnosed based on detection of a *CALR* mutation. In a third patient (Patient 7), without any risk factor for thrombosis on top of CMV nor any

Table 1. Clinical and laboratory characteristics of patients with recent portal venous system thrombosis, according to CMV status.

	n	"CMV positive" group, n = 23	n	"CMV negative" group, n = 53	*p* value pos. *vs.* neg.	n	"CMV unknown" group, n = 297	*p* value pos. *vs* unk.	*p* value neg. *vs.* unk.
Comorbidity									
Gender (female)	23	8 (35)	53	21 (40)	0.799	297	117 (39)	0.825	1.000
Age (years)	23	36 (31–47)	53	51 (38–62)	**0.001**	297	47 (36–59)	**0.002**	0.339
BMI (kg/m^2)	23	28 (26–32)	47	28 (23–32)	0.824	239	26 (23–30)	**0.034**	**0.033**
Obesity (BMI >30 kg/m^2)	23	8 (35)	48	19 (40)	0.797	238	58 (25)	0.314	**0.033**
Alcohol consumption (%)*	23	1 (4)	53	1 (2)	0.516	249	13 (5)	1.000	0.477
Immunosuppression	23	1 (4)	53	2 (4)	1.000	297	19 (6)	1.000	0.752
Positive anti-HCV antibodies	21	0	52	0	–	218	5 (2)	1.000	0.587
Positive HBs antigen	21	0	52	1 (2)	–	218	3 (1)	1.000	0.247
Diabetes	23	4 (17)	53	6 (11)	0.479	231	12 (5)	**0.045**	0.117
Arterial hypertension	23	2 (9)	52	14 (27)	0.125	231	28 (12)	1.000	**0.016**
LSM using Fibroscan®	8	6 (4–7)	31	5 (5–7)	0.875	143	5 (4–7)	0.824	0.718
Clinical characteristics at diagnosis									
No symptoms at diagnosis	23	0	53	8 (15)	0.097	297	39 (17)	**0.031**	0.840
Duration of symptoms	23		45		0.413	198		0.431	0.356
<1 week		10 (44)		24 (45)			98 (50)		
1 week to 1 month		11 (48)		18 (34)			66 (33)		
1–6 months		2 (9)		1 (2)			19 (10)		
>6 months		0		2 (4)			15 (8)		
Body temperature >38.5 °C	23	11 (48)	52	10 (19)	**0.014**	286	57 (20)	**0.006**	1.000
Abdominal pain	23	20 (87)	53	45 (85)	1.000	280	221 (79)	0.434	0.357
Heart rate (bpm)	19	105 (88–107)	49	80 (70–97)	**<0.001**	160	76 (70–88)	**<0.001**	0.196
Laboratory characteristics at diagnosis									
Leukocytes count (G/L)	23	7.6 (6.6–10.9)	52	8.1 (5.2–10.8)	0.374	281	7 (5.5–10.4)	0.117	0.644
Neutrophils (G/L)	22	3.4 (2.5–5.9)	52	4.6 (3.3–7.8)	0.100	274	4.1 (2.8–7.1)	0.261	0.217
Eosinophils (G/L)	21	0.1 (0.0–0.3)	52	0.1 (0.0–0.2)	0.392	274	0.1 (0.1–0.2)	0.694	0.059
Lymphocytes (G/L)	21	3.1 (2.4–4.9)	52	1.6 (1.2–2.2)	**<0.001**	271	1.7 (1.2–2.3)	**<0.001**	0.549
Platelets count (G/L)	23	221 (157–288)	51	276 (202–348)	**0.019**	281	257 (188–330)	**0.044**	0.409
Prothrombin time (%)	20	82 (75–97)	51	85 (75–96)	0.720	278	87 (73–100)	0.702	0.646
Serum ALT (IU/L)	22	99 (55–204)	52	30 (19–46)	**<0.001**	279	43 (26–66)	**<0.001**	0.005
Serum albumin (g/L)	23	34 (31–36)	50	33 (30–38)	0.820	273	37 (33–42)	**0.010**	**<0.001**
Serum bilirubin (μmol/L)	22	9 (7–11)	52	12 (8–16)	0.067	276	10 (7–16)	0.151	0.496
Serum ferritin (μg/L)	19	573 (261–1154)	44	237 (83–508)	**0.007**	189	168 (51–382)	**<0.001**	0.085
Serum CRP (mg/L)	22	76 (22–152)	49	51 (8–162)	0.723	212	30 (5–100)	**0.024**	**0.044**
Triglyceride (mmol/L)	16	1.81 (1.21–2.18)	44	1.1 (0.8–1.5)	**0.005**	200	1.08 (0.74–1.54)	**0.001**	0.504

Data are expressed as median (range) or absolute value (percentage) and were compared using the Mann-Whitney test for quantitative variables, the Chi-square or Fisher's test for qualitative variables. *p* values were calculated between "CMV positive" (pos.), "CMV negative" (neg.) and "CMV unknown" (unk.) groups, and are in bold when $p < 0.05$.

ALT, alanine transaminase; BMI, body mass index; CMV, cytomegalovirus; CRP, C-reactive protein; LSM, liver stiffness measurement.

*Alcohol consumption ≥140 g per week.

Table 2. Risk factors for thrombosis identified at diagnosis of recent portal venous system thrombosis, according to CMV status.

	n	"CMV positive" group, n = 23	n	"CMV negative" group, n = 53	*p* value pos. *vs.* neg.	n	"CMV unknown" group, n = 297	*p* value pos. *vs.* unk.	*p* value neg. *vs.* unk.
Factor V Leiden	23	0	51	2 (4)	1.000	285	18 (6)	0.628	0.750
Prothrombin G20210A gene variant	23	5 (22)	51	2 (4)	**0.010**	286	22 (8)	**0.033**	0.222
Protein C deficiency	23	3 (13)	53	7 (13)	1.000	189	15 (8)	0,423	0.278
Protein S deficiency	23	2 (8)	53	3 (6)	1.000	187	12 (6)	0,332	0.728
Antithrombin deficiency	21	1 (5)	53	6 (11)	0.665	192	10 (5)	1,000	0.122
Myeloproliferative neoplasm	23	1 (4)	52	9 (17)	0.264	287	31 (11)	0.713	0.239
JAK2^{v617f} mutation	21	0	50	7 (14)	0.180	282	27 (10)	0.235	0.319
Antiphospholipid syndrome	22	1 (4)	51	1 (2)	0.515	277	17 (6)	1.000	0.327
Lupus anticoagulant	21	5 (24)	48	4 (8)	0.119	273	31 (11)	0.155	0.801
Anticardiolipin antibodies	20	6 (30)	49	4 (8)	**0.029**	251	12 (5)	**0.001**	0.308
Anti-β2-Gp1 antibodies	20	3 (15)	49	1 (2)	0.070	249	4 (2)	**0.010**	1.000
PNH	20	0	52	1 (2)	1.000	261	1 (0)	1.000	0.305
Behçet's disease	23	0	53	1 (2)	1.000	271	0	–	0.164
Oral contraceptives	8	5 (72)	17	4 (24)	0.061	131	60 (46)	0.254	0.118
Other systemic factors*	23	1 (4)	53	0 (0)	0.307	284	9 (3)	0.655	0.906
Local factors	23	2 (9)	53	12 (23)	0.205	297	67 (23)	0.285	1.000
Personal history of thrombosis	23	2 (9)	53	10 (17)	0.327	297	38 (13)	1.000	0.417
1st degree-relative history of thrombosis	23	5 (22)	53	14 (26)	1.000	297	52 (17)	0.805	0.861
Number of risk factors for thrombosis (0/1/2/3 and more)**	23	10/12/1/0	53	18/27/4/4	0.828	297	95/128/55/19	0.634	0.329

Data are expressed as median (range) or absolute value (percentage) and were compared using the Mann-Whitney test for quantitative variables, the Chi-square or Fisher's test for qualitative variables. *p* values were calculated between "CMV positive" (pos.), "CMV negative" (neg.) and "CMV unknown" (unk.) groups, and are in bold when $p < 0.05$.
CMV, cytomegalovirus; PNH, paroxysmal nocturnal hemoglobinuria.
*Inflammatory bowel disease (n = 2), systemic lupus erythematosus (n = 3), sarcoidosis (n = 1), celiac disease (n = 1), rheumatoid arthritis (n = 1), juvenile idiopathic arthritis (n = 1), psoriasis (n = 1).
**The following risk factors for thrombosis were taken into account: factor V Leiden, prothrombin G20210A gene variant, myeloproliferative neoplasm, confirmed antiphospholipid syndrome, PNH, Behcet's disease, oral contraceptive use, systemic disease, local inflammation or surgery, personal or 1st degree-relative history of thrombosis.

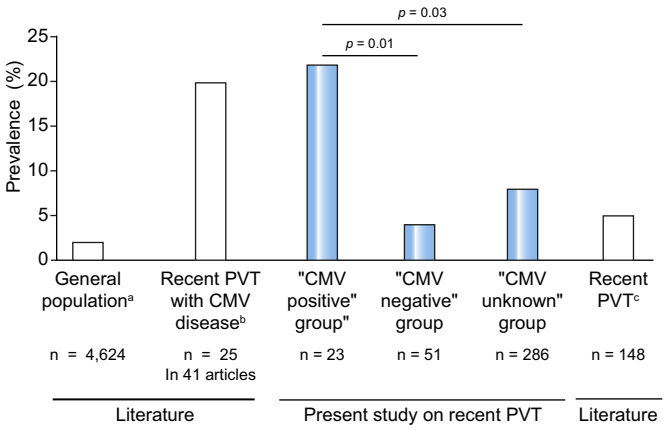

Fig. 1. Prevalence of prothrombin G20210A gene variant in patients with recent portal venous system thrombosis in our study as well as in the literature, according to CMV status. Data were compared using the Fisher's test. [a]Prevalence of prothrombin G20210A gene variant in the general population is based on a study by Rosendaal and colleagues.[73] [b]Prevalence of prothrombin G20210A gene variant in cases of recent PVT and CMV disease reported so far in the literature is based on studies summarized in Table S8. [c]Prevalence of prothrombin G20210A gene variant in patients with recent PVT from the literature based on 2 recent studies on PVT.[28,71] CMV, cytomegalovirus; PVT, portal venous system thrombosis.

cause for cirrhosis, recanalization occurred, and anticoagulation was discontinued at month 22. Six months later, because of a decreasing portal flow velocity, anticoagulation was resumed, and portal flow velocity normalized. No extension of PVT was observed in the "CMV negative" group.

Portal hypertension-related complications

Of the 15 patients in the "CMV positive" group and the 36 patients in the "CMV negative" group who underwent gastroscopy during follow-up, 3 (20%) and 12 (33%) patients had esophageal varices, respectively ($p = 0.506$). Absence of endoscopy was related to complete recanalization of the portal venous system in 12 patients, to loss of follow-up in 6 patients, while there was no explanation in 7 patients (Fig. S5). No gastro-intestinal bleeding occurred during follow-up. The only portal hypertension-related complication was ascites in 2 patients from the "CMV negative" group at 5 and 47 months after PVT. There were 3 deaths during follow-up: one in the "CMV positive" group (Patient 1, 121 months after PVT diagnosis) and 2 in the "CMV negative" group (at 8 and 31 months after PVT diagnosis). Causes of death were extrahepatic malignancies in 2 patients and unknown in the third.

Discussion

The association between recent PVT and CMV disease has long been known. However, data reported so far (45 patients in 40 articles, summarized in Table S8 [30–69]) were too fragmented to have a clear view of the impact of CMV disease on PVT presentation and outcome. Despite the rarity of this association, thanks to the French network on vascular liver diseases, we were able to fill this gap in knowledge. We collected data from 23 well characterized patients with recent PVT associated with CMV disease. Diagnosis of CMV disease was based on international guidelines as well as on data review by an expert virologist: 15 patients had confirmed CMV disease and 8 patients had highly

Table 3. Multivariate analysis using Cox regression model of variables associated with complete recanalization of portal venous system thrombosis at 24 months in 62 patients with recent PVT and follow-up imaging available (20 patients from the "CMV positive" group and 42 from the "CMV negative" group).

Variable	Hazard ratio	95% CI	*p value*
Abdominal pain	0.581	0.188–1.802	0.348
Number of occluded segments of the portal venous system*	0.591	0.403–0.866	**0.007**
Serum ALT (IU/L)	1.002	0.999–1.004	0.219

This analysis included variables associated with the persistence of portal venous system thrombosis at 24 months by univariate analysis, with *p* value <0.05 and with available data for more than 95% of the patients. *p* value <0.05 are written in bold. Regarding imaging features, only number of completely occluded segments was included in the analysis and not each specific location.
Variables with hazard ratio >1 are associated with complete recanalization at 24 months.
ALT, alanine aminotransferase; CI, confidence interval; CMV, cytomegalovirus.
*The following segments were considered: right portal branch, left portal branch, portal trunk, splenic vein, superior mesenteric vein.

likely CMV disease attested by detectable plasma anti-CMV IgM, as well as either an elevated lymphocyte/neutrophil ratio or detectable Downey cells in 7 out of these 8 patients. Patients with CMV disease were compared with 2 control groups: patients with virological tests ruling out CMV disease ("CMV negative" group; n = 53) and a large group of patients with unknown CMV status ("CMV unknown" group; n = 297) having similar geographic origin and date of inclusion as patients from the "CMV positive" group. The large number of patients included in the "CMV unknown" group is evidence of the unsystematic nature of CMV testing across centers over the study period, which might have caused a bias. Yet, patient characteristics in the 2 control groups were similar, suggesting that most patients with unknown CMV status did not have CMV disease. Moreover, patients from the "CMV positive" and "CMV unknown" group were included in multiple French centers, limiting the risk of bias due to specific local recruitment.

The first major finding of this study was that CMV disease does not influence initial extension nor outcome of recent PVT. Indeed, we observed that the number of segments occluded in the portal venous system was not different between patients with CMV disease and patients in the 2 control groups. Moreover, the cumulative incidence of complete recanalization was similar between patients in the "CMV positive" and "CMV negative" groups, with figures in line with those previously reported in a prospective European multicentric study.[5] The number of completely occluded segments at PVT diagnosis was the only variable independently associated with a lower incidence of recanalization. This information was lacking in the literature and one could have thought that an acute event, like CMV disease, would have been associated with a better outcome of PVT. Our data do not allow us to draw conclusions with regard to anticoagulation initiation since only 1 out of 23 CMV-positive patients did not receive anticoagulation at PVT diagnosis, nor on anticoagulation duration since anticoagulation was interrupted in only 6 of these patients. Yet, analysis of individual cases suggests that caution is needed when considering discontinuation of anticoagulation since 1 patient without any additional risk factor for thrombosis besides CMV infection had a decreasing portal flow velocity following anticoagulation interruption that normalized after anticoagulation was resumed. Our results did not allow us to test the effect of anti-CMV antiviral treatment as only 3 patients received such treatment, and they all had a severe presentation or extended thrombosis. The available literature regarding antiviral treatment for thrombosis in other vascular beds in patients with CMV disease is also limited and thus does not allow for extrapolation.[13–16,70]

The second major finding of this study is that more than half of the patients with CMV-associated PVT had another risk factor for thrombosis. The number of thrombosis risk factors, regardless of the presence of CMV disease, was not different between the 3 groups. This suggests that CMV disease is not a strong risk factor for PVT and may rather be a trigger for PVT in susceptible patients. This view is reinforced by the rarity of the association of CMV disease with PVT, contrasting with the high incidence of CMV infection in the general population (1% per year in young adults approximately).[20] As a practical consequence, diagnosing CMV disease in a patient with recent PVT should not deter clinicians from performing comprehensive screening for risk factors of thrombosis.

The third major finding of this study is the strong link between CMV-associated recent PVT and the prothrombin G20210A gene variant (Fig. 1). Indeed, in our study, the prothrombin G20210A gene variant was detected in 22% of patients with CMV-associated recent PVT *vs.* 4% and 8% in the 2 control groups. Detailed analysis of available literature supports our findings, since 5 out of the 25 patients (20%) with CMV-associated recent PVT, for whom data was available, had the prothrombin G20210A gene variant, *vs.* 6% in all patients with PVT in recent studies.[28,71,72] The prevalence of the prothrombin G202010A gene variant in the general western European population is around 2% (Fig. 1).[73] The association between CMV-associated recent PVT and the prothrombin G20210A gene variant could be explained by their synergistic effect on thrombin generation: the prothrombin G20210A gene variant is associated with increased plasma prothrombin levels and dysthrombinaemia with unstable prothrombin that is more easily activated[74]; the CMV surface contains procoagulant phospholipids, allowing for assembly of the prothrombinase enzyme complex, and thus favoring production of thrombin.[75–77] This effect was observed *in vitro* with infected cells and viral particles. Another hypothesis is that CMV exerts a prothrombotic effect via the transient presence of antiphospholipid antibodies secondary to infection of endothelial cells, which was observed at PVT diagnosis in our study and in the literature.[78,79] However, CMV disease was not associated with antiphospholid syndrome, as the presence of antiphospholipid antibodies was similar in the 3 groups at 12 weeks, as described in the literature.

In conclusion, CMV disease was associated with recent PVT, but did not influence the extension, localization nor recanalization of thrombosis. Accordingly, diagnosis of CMV disease should not influence clinical decisions on PVT management. Other risk factors for thrombosis are often present so that identification of CMV disease does not obviate the need for a complete work-up for risks factors for thrombosis. In particular, a special link exists between the prothrombin G20210A gene variant and CMV disease.

Abbreviation
CMV, cytomegalovirus; PVT, portal venous system thrombosis.

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Conflict of interest
Authors declare no conflict of interest related to the present study.

Please refer to the accompanying ICMJE disclosure forms for further details.

Authors' contributions
PER, DV and CDB designed the study. CDB and PER wrote the manuscript. AP, IOH, SD, CDB, JPC, PS, OG, OC, KZ, and AP collected patients' data. NFH and YY provided virological insight. All authors read and critically revised the manuscript.

Data availability statement
The datasets generated and analyzed during the current study are not publicly available but are available from the corresponding author upon reasonable request.

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